

15. Intensive Care Society. Standards for the care of adult patients with a temporary Tracheostomy. 2014. Available from www.ics.ac.uk/EasySiteWeb/GatewayLink.aspx?alid=2212 (Accessed 3 January 2015)
16. Ford ES, Maynard LM, Li C. Trends in mean waist circumference and abdominal obesity among US adults, 1999–2012. *JAMA* 2014; **312**: 1151–3
17. Templeton R, Webster K, McGrath BA. Patient safety incidents associated with displaced or obstructed tracheostomies: comparison of levels of harm between critical care and ward environments. *Br J Anaesth* 2011; **107**: 834–5
18. McGrath BA, Bates L, Atkinson D, Moore JA. Multidisciplinary guidelines for the management of tracheostomy and laryngectomy airway emergencies. *Anaesthesia* 2012; **68**: 1025–41
19. Cameron TS, McKinstry A, Burt SK, et al. Outcomes of patients with spinal cord injury before and after introduction of an interdisciplinary tracheostomy team. *Crit Care Resusc* 2009; **11**: 14–9
20. Pandian V, Miller CR, Mirski MA, et al. Multidisciplinary Team Approach in the Management of Tracheostomy Patients. *Otolaryngol Head Neck Surg* 2012; **147**: 684–91
21. Cetto R, Arora A, Hettige R, et al. Improving tracheostomy care: a prospective study of the multidisciplinary approach. *Clin Otolaryngol* 2011; **36**: 482–8
22. Speed L, Harding KE. Tracheostomy teams reduce total tracheostomy time and increase speaking valve use: A systematic review and meta-analysis. *J Crit Care* 2013; **28**: 216.e1–10
23. McGrath BA, Wallace S. The UK National Tracheostomy Safety Project and the role of speech and language therapists. *Curr Opin Otolaryngol Head Neck Surg* 2014; **22**: 181–7

British Journal of Anaesthesia 115 (2): 158–61 (2015)
Advance Access publication 3 June 2015 · doi:10.1093/bja/aeu167

Haemostatic efficacy of fibrinogen concentrate: is it the threshold or the timing of therapy?

D. Bolliger^{1,*} and K. A. Tanaka²

¹ Department of Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, CH-4031 Basel, Switzerland, and

² Department of Anesthesiology, Cardiothoracic Anesthesia Division, University of Maryland, Suite S8D12, Baltimore, MD, USA

*Corresponding author. E-mail: daniel.bolliger@usb.ch

Fibrinogen is the key substrate of thrombin in haemostatic clot formation, and its plasma concentration is highly susceptible to blood loss and haemodilution;^{1–3} therefore, it has been recognized as a primary target of coagulation therapy in the management of perioperative major bleeding.^{2–7} Human plasma-derived fibrinogen concentrate is convenient to use because it is lyophilized and quickly reconstituted for i.v. injection. In addition, it is simple to monitor the dose because fibrinogen concentrate increases plasma fibrinogen concentration in a dose-dependent manner⁸ and increases fibrin-specific clot formation (FIBTEM) on thromboelastometry.^{9–10} However, there is no consensus on the minimal fibrinogen concentration or FIBTEM value that is required for perioperative haemostasis,¹¹ and there are concerns regarding overuse and misuse.^{12–13} The value of FIBTEM-based fibrinogen interventions has been evaluated previously in both prospective studies and retrospective analyses (Table 1).^{14–17–19} However, it is yet unknown whether a low normal fibrinogen concentration (1.5 g litre⁻¹) is adequate for haemostasis in the perioperative setting or whether higher concentrations of fibrinogen might be required to reduce bleeding.

In this issue of the *British Journal of Anaesthesia*, Haas and colleagues¹⁵ shed new light on the perioperative fibrinogen replacement strategy. The authors performed a well-designed randomized controlled study in paediatric patients undergoing craniosynostosis and scoliosis surgery. Patients were randomized to receive therapy with fibrinogen concentrate based on a high (13 mm) or low target value (8 mm) of FIBTEM maximal

clot firmness (MCF). The authors found that intraoperative fibrinogen intervention using the higher threshold significantly reduced bleeding by ~67% and transfusion requirements by nearly 50% compared with the lower threshold value in craniosynostosis surgery. In scoliosis surgery, however, the extent of bleeding was similar between both groups, and only a trend for reduced transfusion with the higher threshold was found.

The two thresholds, 8 and 13 mm of FIBTEM MCF, used in this study represent the lower and upper target range in the European guidelines for the treatment of massive perioperative bleeding.⁶ They are also likely to correspond to the minimal fibrinogen concentration (1.5 g litre⁻¹) recommended by the European guidelines⁶ and the median concentration of fibrinogen (2.35 g litre⁻¹) for this age group.²⁰ Those who were randomized to the higher threshold received intervention early because their baseline FIBTEM MCF values were 10–11 mm (corresponding to plasma concentrations of about 1.8–2.0 g litre⁻¹).²¹ It can be speculated that plasma fibrinogen concentrations were maintained at above 2.0 g litre⁻¹ in the high-threshold group when intraoperative bleeding occurred. In the low-threshold group, however, plasma fibrinogen could be decreased to below 1.5 g litre⁻¹ as bleeding continued. It is thus important to consider the timing of therapy in addition to the optimal threshold. Nakayama and colleagues¹⁶ recently reported a prospective randomized study of conventional vs thromboelastometry-guided haemostatic intervention in paediatric cardiac surgery. In their study, the FIBTEM threshold was set rather low at 5 mm for

Table 1 Fibrin-specific clot formation thresholds used by published prospective randomized studies. A_{10/15}, amplitude after 10/15 min; ACT, activated clotting time; FC, fibrinogen concentrate; FFP, fresh frozen plasma; FIBTEM, fibrin-specific clot formation; MCF, maximal clot formation; NA, not available; RBC, red blood cell; ROTEM, rotational thromboelastometry

Author, yr	Study setting	Intervention and trigger values		Key findings	Fibrinogen concentrations after surgery
		Intervention group	Control group		
Girdauskas and colleagues, 2010 ¹⁴	56 adult patients undergoing complex cardiac surgery	FC administered if FIBTEM MCF<8 mm (n=27)	FC administered if plasma fibrinogen concentration <1.2 g litre ⁻¹ (n=29)	ROTEM-guided transfusion is associated with decreased use of allogeneic blood products	NA
Haas and colleagues, 2015 ¹⁵	49 paediatric patients undergoing craniostomosis or scoliosis surgery	FC administered if FIBTEM MCF<13 mm (n=27)	FC administered if FIBTEM MCF<8 mm (n=22)	Higher trigger value reduced bleeding and RBC transfusion in craniostomosis but not scoliosis surgery	NA
Nakayama and colleagues, 2014 ¹⁶	100 paediatric patients undergoing cardiac surgery	FFP administered if FIBTEM A ₁₀ <5 mm (n=50)	FFP administered if ACT≥150 s after protamine 0.5 mg kg ⁻¹ (n=50)	ROTEM-guided transfusion reduced bleeding and RBC transfusion	1.65 g litre ⁻¹ (intervention) vs 1.25 g litre ⁻¹ (control)
Rahe-Meyer and colleagues, 2013 ⁷	61 bleeding adult patients undergoing complex cardiac surgery	FC administered if FIBTEM MCF<22 mm (n=29)	NaCl 0.9% (placebo) administered if FIBTEM MCF<22 mm (n=32)	FC reduced the need for allogeneic blood products	2.60 g litre ⁻¹ (intervention) vs 1.89 g litre ⁻¹ (control)
Weber and colleagues, 2012 ¹⁷	100 bleeding adult patients undergoing cardiac surgery	FC administered if FIBTEM A ₁₀ ≤10 mm (n=50)	FC administered if plasma fibrinogen concentration <1.5 g litre ⁻¹ (n=50)	ROTEM-guided transfusion reduced transfusion of allogeneic blood products and improved outcome	2.29 g litre ⁻¹ (intervention) vs 1.97 g litre ⁻¹ (control)

10 min amplitude (A_{10}), but the FIBTEM-based protocol resulted in early plasma transfusion compared with the conventional therapy. The reduced red blood cell transfusion and postoperative blood loss in the FIBTEM group are partly explained by the higher fibrinogen concentrations than those with the conventional therapy (1.65 vs 1.25 g litre⁻¹). Importantly, total amounts of plasma and platelet transfusion were not different between both groups.¹⁶ Likewise, Haas and colleagues¹⁵ found that total administered amounts of fibrinogen and factor XIII concentrate, and of plasma and platelet transfusion were comparable between their two groups. It is thus important to optimize the threshold and the timing of haemostatic intervention because they interact closely with each other.

There have been previous clinical studies that involved prophylactic administration of fibrinogen concentrate to maintain high normal fibrinogen concentrations for cardiac surgery²² and for postpartum haemorrhage.²³ However, major concerns regarding the prophylactic substitution are that bleeding attributable to a surgical cause cannot be stopped by fibrinogen, and administered fibrinogen can quickly be lost in haemorrhage and haemodilution.²⁴ The efficacy of prophylactic fibrinogen substitution may be strongly influenced by the surgical technique, extent of vascular injury, and intraoperative blood loss. The study by Haas and colleagues¹⁵ was, therefore, terminated prematurely because of the surgical staff change. A larger multicentre study should be considered to validate a FIBTEM MCF of 13 mm as a potential haemostatic target to reduce allogeneic blood exposure, postoperative intensive care stay, and other transfusion-related complications.

Besides the limitations of a small single-centre study, the study of Haas and colleagues¹⁵ is underpowered for any safety analysis. Overdosing of fibrinogen concentrate might be associated with thromboembolic complications, especially in patients with cardiovascular diseases.^{25–26} There is a paucity of data on the safety of any factor concentrate usage in paediatric acquired coagulopathy, but the thromboembolic risk of paediatric patients appears to be lower than that of adults.²⁷ In adult cardiac surgery, the administration of fibrinogen targeting a plasma concentration of ~2 g litre⁻¹ (corresponding to a FIBTEM MCF of ~10 mm) was not associated with worse 30 day and 1 yr outcomes compared with patients without administration of fibrinogen concentrate.⁴

In summary, the work of Haas and colleagues¹⁵ has provided further evidence that maintaining fibrinogen at above 2.0 g litre⁻¹ might be more advantageous in reducing bleeding volumes and red blood cell transfusion than on-demand therapy after fibrinogen concentration reduces to below 1.5 g litre⁻¹. The extrapolation of their findings to general paediatric surgical populations should be done cautiously, because this was a single-centre study with a limited sample size in very specific surgical procedures. At present, a routine prophylactic administration of fibrinogen concentrate is not recommended, but a fibrinogen concentration below 2.0 g litre⁻¹ or FIBTEM MCF below 10 mm seems to be an acceptable target to commence early haemostatic intervention in patients who are at increased risk for profuse bleeding in major surgery.

Declaration of interests

D.B. has received honoraria for independent lectures and an unrestricted research grant from CSL Behring AG, Berne, Switzerland. K.A.T. is currently involved in a clinical study sponsored by a manufacturer of rotational thromboelastometry (TEM Innovations, Munich, Germany).

References

- Bolliger D, Gonsahn M, Levy JH, Williams WH, Tanaka KA. Is preoperative fibrinogen predictive for postoperative bleeding after coronary artery bypass grafting surgery? *Transfusion* 2009; **49**: 2006–7
- Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. *Anesthesiology* 2010; **113**: 1205–19
- Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg* 1995; **81**: 360–5
- Fassl J, Lurati Buse G, Filipovic M, et al. Perioperative administration of fibrinogen does not increase adverse cardiac and thromboembolic events after cardiac surgery. *Br J Anaesth* 2015; **114**: 225–34
- Kozek-Langenecker S, Sørensen B, Hess JR, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care* 2011; **15**: R239
- Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2013; **30**: 270–382
- Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology* 2013; **118**: 40–50
- Solomon C, Pichlmaier U, Schoebl H, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. *Br J Anaesth* 2010; **104**: 555–62
- Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. *Br J Anaesth* 2009; **102**: 793–9
- Tanaka KA, Esper S, Bolliger D. Perioperative factor concentrate therapy. *Br J Anaesth* 2013; **111** Suppl 1: i35–49
- Bolliger D, Mauermann E, Tanaka KA. Thresholds for perioperative administration of hemostatic blood components and coagulation factor concentrates: an unmet medical need. *J Cardiothorac Vasc Anesth* 2015; **29**: 768–76
- Dietrich W, Faraoni D, von Heymann C, et al. ESA guidelines on the management of severe perioperative bleeding: comments on behalf of the Subcommittee on Transfusion and Haemostasis of the European Association of Cardiothoracic Anaesthesiologists. *Eur J Anaesthesiol* 2014; **31**: 239–41
- Faraoni D, Dinardo JA. Pre-operative fibrinogen supplementation in cardiac surgery patients. More is not always better. *Acta Anaesthesiol Scand* 2015; **59**: 409–13
- Girdauskas E, Kempfert J, Kuntze T, et al. Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. *J Thorac Cardiovasc Surg* 2010; **140**: 1117–24
- Haas T, Spielmann N, Restin T, et al. Efficacy of maintaining higher fibrinogen levels for reduction of transfusion requirements during major paediatric surgery. A randomized, controlled clinical trial. *Br J Anaesth* 2015; in press
- Nakayama Y, Nakajima Y, Tanaka KA, et al. Thromboelastometry-guided intraoperative haemostatic management reduces bleeding and red cell transfusion after paediatric cardiac surgery. *Br J Anaesth* 2015; **114**: 91–102
- Weber CF, Görlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy

- in coagulopathic cardiac surgery patients. *Anesthesiology* 2012; **117**: 531–47
18. Fassl J, Matt P, Eckstein F, et al. Transfusion of allogeneic blood products in proximal aortic surgery with hypothermic circulatory arrest: effect of thromboelastometry-guided transfusion management. *J Cardiothorac Vasc Anesth* 2013; **27**: 1181–8
 19. Görlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. *Anesthesiology* 2011; **115**: 1179–91
 20. Oswald E, Stalzer B, Heitz E, et al. Thromboelastometry (ROTEM) in children: age-related reference ranges and correlations with standard coagulation tests. *Br J Anaesth* 2010; **105**: 827–35
 21. Ogawa S, Szlam F, Bolliger D, Nishimura T, Chen EP, Tanaka KA. The impact of hematocrit on fibrin clot formation assessed by rotational thromboelastometry. *Anesth Analg* 2012; **115**: 16–21
 22. Karlsson M, Ternström L, Hyllner M, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost* 2009; **102**: 137–44
 23. Wikkelsø AJ, Edwards HM, Afshari A, et al. Pre-emptive treatment with fibrinogen concentrate for postpartum haemorrhage: randomized controlled trial. *Br J Anaesth* 2015; **114**: 623–33
 24. Bader SO, Ranier G. Is it necessary to maintain fibrinogen during hypothermia and major bleeding in vascular surgery? *J Cardiothorac Vasc Anesth* 2012; **26**: e54–5
 25. Hicks RC, Ellis M, Mir-Hasene R, et al. The influence of fibrinogen concentration on the development of vein graft stenoses. *Eur J Vasc Endovasc Surg* 1995; **9**: 415–20
 26. Kaski JC, Fernández-Bergés DJ, Consuegra-Sánchez L, et al. A comparative study of biomarkers for risk prediction in acute coronary syndrome-Results of the SIESTA (Systemic Inflammation Evaluation in non-ST-elevation Acute coronary syndrome) study. *Atherosclerosis* 2010; **212**: 636–43
 27. Guzzetta NA, Russell IA, Williams GD. Review of the off-label use of recombinant activated factor VII in pediatric cardiac surgery patients. *Anesth Analg* 2012; **115**: 364–78

British Journal of Anaesthesia **115** (2): 161–3 (2015)
doi:10.1093/bja/aev214

Reliable critical care: making it easy to do the right thing

R. Sundaram¹ and K. D. Rooney^{1,2,*}

¹ Department of Anaesthesia and Intensive Care Medicine, Royal Alexandra Hospital, Paisley PA2 9PN, UK, and

² Institute of Care and Practice Improvement, University of the West of Scotland, Paisley PA1 2BE, UK

*Corresponding author. E-mail: kevin.rooney@uws.ac.uk

Sir Muir Gray, Director of the NHS Chief Knowledge Office, hypothesized that ‘The application of what we know will have a bigger impact than any drug or technology likely to be introduced in the next decade.’ He recognized that blind investment in new drugs and technologies that provide only a modest improvement in efficacy may cost more lives than it saves, because this investment will consume scarce resources needed for improved delivery of care. Therefore, it can be argued from a health, economic, and moral standpoint that we should spend less on new technology and new drugs and more on improving systems for delivery of care¹ and turning knowledge into action.

Whilst few of us would disagree that robust evidence from clinical trials should be implemented to improve patient care, it has become apparent that a gap exists and that the translation of evidence into routine practice is not as widespread and easily done as one would have expected. Evidence suggests that it takes on average 17 years for research evidence to reach clinical practice.² This is a remarkably slow and inefficient process. Indeed, it took 13 years for cardiologists to recommend thrombolysis for the treatment of acute myocardial infarction after the publication of randomized controlled trials showed therapeutic benefit.³ Furthermore, Lomas and colleagues⁴ calculated a 5 year gap between publication of guidelines and changes to routine practice in Western health-care systems. Although the paucity of robust and high-quality evidence in critical care used to be cited as a reason for the lack of change in practice, critical care research in the

last 10 years has been inundated with a number of practice-changing headlines, leaving clinicians with the responsibility of ensuring that these are incorporated into everyday practice to enable patients to receive safe, effective, and person-centred care.

In 2000, the acute respiratory distress syndrome (ARDS) network study demonstrated conclusively and unarguably that limiting tidal volume to <6 ml kg⁻¹ predicted body weight (PBW) and end-inspiratory pressure to not more than 30 cm H₂O, compared with patients ventilated with higher tidal volumes (>12 ml kg⁻¹ PBW), significantly reduces mortality in acute lung injury and ARDS, with a number needed to treat of 11 patients to save one life.⁵ No special equipment or expertise was required to achieve this benefit. Despite the perceived relative simplicity of implementing low-tidal volume ventilation, a number of studies published in the last 10 years reveal a disappointing failure of clinicians to adopt and implement this piece of evidence.^{6–8}

In a simple yet elegantly designed and conducted service evaluation study in this issue of the *BJA*, Bourdeaux and colleagues⁹ have demonstrated how a large screen configured to display information routinely collected from a clinical information system resulted in a significant and sustained improvement in the use of evidence-based ventilation practice and reduced unwarranted tidal volume variation with improved reliability. In a mixed medical and surgical intensive care unit in a UK teaching hospital, two similar cohorts of patients on controlled mechanical